REMARKS

A typographical error has been corrected in the amendment effected to page 50, in the paragraph beginning at line 21. Claim 46 has also been clarified so as to be directed to a crystal of the recited compound.

The amendment is supported in the specification at page 105, lines 2-5.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**Version with markings to showing changes made**."

Favorable action on the merits is solicited.

Respectfully submitted,

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wherein $X^{a'}$ is $OCOR^a$ can be produced from among the compounds (alla). These reactions are all carried out under basic conditions. When a compound wherein M^a is alkaline metal atom or alkaline earth metal atom is used as compound (all'), a base does not need to be added, because they are basic, but when a compound wherein M^a is hydrogen atom is used as compound (all'), a base is generally added to the reaction mixture. Examples of the preferable "base" include tertiary amines such as trimethylamine, triethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene etc., heterocyclic aromatic organic bases such as pyridine, picoline etc. and the like.

Page 44, line 3, please rewrite the paragraph as follows:

The "optionally substituted thiol" of the "phenyl substituted by optionally substituted thiol" represented by R^{a6a} is exemplified by those similar to the aforementioned "optionally substituted thiol" represented by R^{a4}, R^{a5}, R^{a7} or R^{a8}.

Page 50, line 21, please rewrite the paragraph as follows:

The "substituent" of the "optionally substituted aromatic heterocyclic group" represented by R^{b16} is exemplified by 1 to 5 from the aforementioned "optionally substituted hydroxy", "optionally substituted thiol", "optionally substituted amino", "optionally substituted hydrocarbon group", "optionally substituted heterocyclic group", "acyl" and the like represented by R^{b4} or R^{b5}. Of these, optionally substituted hydrocarbon group is preferable, and C_{2-6} alkenylene substituted by optionally substituted C_{6-14} aryl is more preferable.

Page 60, line 19, please rewrite the paragraph as follows:

When the compound (cVI) is on the market, a commercially available product thereof may be used as it is, or compound (cVI) may be produced according to a method known *per se*, a method analogous thereto, and the like.

Version with Markings to Show Changes Made

IN THE CLAIMS

Claim 46. (Amended) A crystal of 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole.

the like.

The "ring" may have 1 to 5, preferably 1 to 3, for example, the above-mentioned substituents at substitutable position(s). When the number of the substituents is two or more, the respective substituents may be the same or different.

The "halogen" represented by X^{b1} and X^{b2} is exemplified by fluoro, chloro, bromo and iodo.

The "substituent" of the "optionally substituted hydroxy" represented by R^{b4}, R^{b5}, R^{b7} and R^{b8} is exemplified by those similar to the "substituent" of the aforementioned "optionally substituted hydrocarbon group" and the like.

The "substituent" of the "optionally substituted thiol" represented by R^{b4}, R^{b5}, R^{b7} and R^{b8} is exemplified by those similar to the "substituent" of the aforementioned "optionally substituted hydrocarbon group" and the like.

The "alkyl" of the "optionally substituted alkyl" represented by R^{b6} is exemplified by C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl etc.) and the like.

The "substituent" of the "optionally substituted alkyl" is exemplified by 1 to 5 from those similar to the "substituent" of the aforementioned "optionally substituted hydrocarbon group" and the like.

The "substituent" of the "optionally substituted phenyl" represented by R^{b6} is exemplified by 1 to 5 from those similar to the "substituent" of the aforementioned "optionally substituted hydrocarbon group" and the like.

The "aromatic group" of the "optionally substituted aromatic group" ~~and "optionally substituted aromatic group"~~ represented by R^{b9} is exemplified by C_{6-14} aryl, 5 to 14-membered heterocyclic group and the like.

The "C_{6-14} aryl" is exemplified by phenyl, 1-naphthyl, 2-naphthyl, 2-biphenylyl, 3-biphenylyl, 4-biphenylyl, 2-anthryl and the like. Of these, phenyl is preferable.

The "alkenylene" of the "optionally substituted alkenylene" represented by R^{b12} is exemplified by C_{2-10} alkenylene such as $-CH=CH-$, $-CH_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, $-CH=CH-CH=CH-CH_2-CH_2-$, $-CH=CH-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-CH=CH-CH=CH-CH_2-CH_2-CH_2-$, $-CH=CH-CH=CH-CH=CH-CH_2-CH_2-$, $-CH=CH-CH=CH-CH=CH-CH_2-$, $-CH=CH-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$, $-CH=CH-CH=CH-CH_2-CH_2-CH_2-CH_2-$, $-CH=CH-CH=CH-CH=CH-CH_2-CH_2-$, $-CH=CH-CH=CH-CH=CH-CH=CH-$ and the like.

The "substituent" of the "optionally substituted alkenylene" is exemplified by 1 to 5, preferably 1 to 3, from those similar to the "substituent" of the aforementioned "optionally substituted hydrocarbon group" and the like. When the number of the substituents is two or more, the respective substituents may be the same or different.

The "alkynylene" of the "optionally substituted alkynylene" represented by R^{b12} is exemplified by C_{2-10} alkynylene such as

$$-C\equiv C-,\quad -CH_2-C\equiv C-,\quad -CH_2-C\equiv C-CH_2-CH_2-$$

and the like.

The "substituent" of the "optionally substituted alkynylene" is exemplified by 1 to 5, preferably 1 to 3, from those similar to the "substituent" of the aforementioned "optionally substituted hydrocarbon group" and the like. When the number of the substituents is two or more, the respective substituents may be the same or different.

The "aromatic group" may have 1 to 5, preferably 1 to 3, for example, the above-mentioned substituents at substitutable position(s). When the number of the substituents is two or more, the respective substituents may be the same or different.

The "lower alkyl" represented by R^{c1}, R^{c2}, R^{c3}, R^{c4} and R^{c5} is exemplified by C_{1-6} alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl etc.) and the like.

The "substituent" of the "optionally substituted phenyl",

secondary or tertiary alcohol in the presence of a base to give compound (aIa) or (aIb).

The amount of use of compound (aIII) is about 0.1-10 mol, preferably about 0.5-3.0 mol, per 1 mol of compound (aII).

The amount of use of the base is about 0.1-10 mol, preferably about 0.5-3.0 mol, per 1 mol of compound (aII).

Examples of the "base" include hydride of alkali metal or alkaline earth metal (e.g., lithium hydride, sodium hydride, potassium hydride, calcium hydride etc.), amide of alkali metal or alkaline earth metal (e.g., lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyl disilazide, sodium hexamethyl disilazide, potassium hexamethyl disilazide etc.), hydroxide of alkali metal or alkaline earth metal (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide etc.), metal hydrocarbon (e.g., butyllithium, tert-butyllithium etc.), lower alkoxide of alkali metal or alkaline earth metal (e.g., sodium methoxide, sodium ethoxide, potassium tert-butoxide etc.), carbonate of alkali metal or alkaline earth metal (e.g., sodium hydrogen carbonate, sodium carbonate, potassium carbonate etc.), organic base [amines (e.g., triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene) etc.), organic base of basic heterocyclic compound (e.g., pyridine, imidazole, 2,6-lutidine etc.) etc.], and the like. Of these, hydroxide of alkali metal or alkaline earth metal is preferable.

Examples of the "secondary or tertiary alcohol" include secondary alcohol such as isopropyl alcohol, 2-butanol etc., tertiary alcohol such as tert-butanol, 2-methyl-2-butanol etc., and the like. Of these, tertiary alcohol is preferable.

This reaction may be carried out in a solvent inert to the reaction, besides secondary or tertiary alcohol. Examples of the "inert solvent" include halogenated hydrocarbons (e.g.,

and a salt thereof can be produced. Examples of the salt include those similar to the salt of a compound of the above-mentioned formula (aIa). This deprotection can be carried out under mild conditions from among the general means of deprotecting protected hydroxy group, and is industrially advantageous. For example, compound (aIe) is reacted in the presence of an acid to remove t-butyl, which is a hydroxy protecting group according to a conventional method for deprotection. Examples of the "acid" include organic acids such as acetic acid, trifluoroacetic acid, trichloroacetic acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, toluenesulfonic acid and the like, and mineral acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, chloric acid, perchloric acid, bromic acid, perbromic acid, iodic acid, periodic acid and the like. The solvent may be or may not be used. The acid may be or may not be diluted. When it is to be diluted, it is preferably diluted to 0.01 N-5 N. The reaction temperature is generally from 0°C to 100°C, preferably from 20°C to 70°C. The reaction time is generally about 0.1 hour to 5 hours, preferably about 0.1 hour to 2 hours.

The compound (aIe) can be produced by reacting, from among the compounds (aII), a compound [compound (aIIa)] wherein R^{a1} and R^{a2} are both hydrogen atoms and R^{a3} is 3-[4-(tert-butoxyphenyl)]-propyl and triazole.

The compound (aIIa) can be produced by, for example, reacting compound (aII') and compound (aa), (ab) ~~or~~ (ac) or (ad) under basic conditions. That is, by reacting compound (aII') and compound (aa) or (ab), a compound wherein $X^{a'}$ is halogen can be produced from among the compounds (aIIa), and by reacting compound (aII') and compound (ac), a compound wherein $X^{a'}$ is OSO_2R^a can be produced from among the compounds (aIIa), and by reacting compound (aII') and compound (ad), a compound wherein $X^{a'}$ is $OCOR^a$ can be produced from among the compounds (aIIa). These reactions are all carried out under basic conditions.

When a compound wherein M^a is alkaline metal atom or alkaline earth metal atom is used as compound (aII'), a base does not need to be added, because they are basic, but when a compound wherein M^a is hydrogen atom is used as compound (aII') ~~(IIa')~~, a base is generally added to the reaction mixture. Examples of the preferable "base" include tertiary amines such as trimethylamine, triethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene etc., heterocyclic aromatic organic bases such as pyridine, picoline etc. and the like.

When compound (aII') and compound (aa) or (ab) are reacted, the reaction generally proceeds in a solvent inert to the reaction under basic conditions. Alternatively, the "base" may be used as a solvent. Examples of the "solvent" include halogenated hydrocarbons such as dichloromethane, dichloroethane and the like, aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as diethyl ether, diisopropy ether, tert-butylmethyl ether, tetrahydrofuran and the like, nitriles such as acetonitrile, propionitrile, isopropionitrile and the like, and esters such as ethyl acetate, isopropyl acetate and the like. The reaction temperature is generally from 0°C to 100°C, preferably 10°C to 70°C.

The compound (aII') and compound (ac) or (ad) can be reacted according to a conventional method, which proceeds in an organic solvent generally inert to the reaction under basic conditions. Alternatively, the "base" may be used as a solvent. Examples of the "organic solvent inert to the reaction" include halogenated hydrocarbons such as dichloromethane, dichloroethane and the like, aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as diethyl ether, diisopropy ether, tert-butylmethyl ether, tetrahydrofuran and the like, nitriles such as acetonitrile, propionitrile, isopropionitrile and the like, esters such as ethyl acetate, isopropyl acetate and the like, and the like.

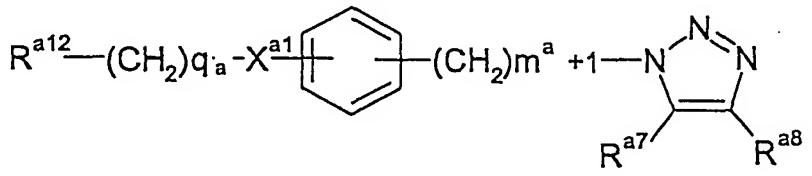
aforementioned "optionally substituted hydroxy" represented by R^{a4} or R^{a5}.

The "optionally substituted thiol" of the "phenyl substituted by optionally substituted thiol" represented by R^{a6a} is exemplified by those similar to the aforementioned "optionally substituted thiol" represented by R^{a4}, ~~or~~ R^{a5}, R^{a7} or R^{a8}.

For example, compound (aIc) or (aId) is subjected to deprotection known *per se*, where necessary, then reacted with a compound of the formula

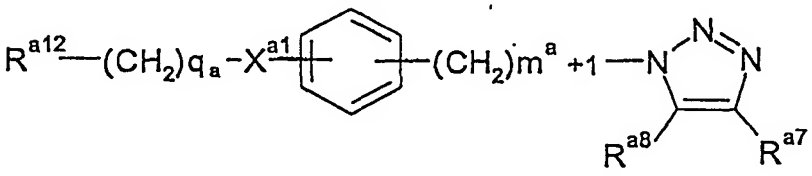
$$R^{a12}-(CH_2)_{qa}-W^a$$

wherein R^{a12} is an optionally substituted aromatic heterocyclic group, qa is an integer of 1 to 5, and W^a is a leaving group, or a salt thereof [hereinafter to be briefly referred to as compound (aIV)] to give a compound of the formula



(aVa)

or



(aVb)

wherein X^{a1} is an oxygen atom or a sulfur atom, and other symbols are as defined above, or a salt thereof.

When the compound (aIV) is on the market, a commercially available product thereof may be used as it is, or compound (aIV) may be produced according to a method known *per se*, a method analogous thereto, and the like.

The "leaving group" represented by W^a is exemplified by

substituted by C_{1-6} alkyl, such as p-toluenesulfonyloxy etc.) and the like.

The "aromatic heterocyclic group" of the "optionally substituted aromatic heterocyclic group" represented by R^{b16} is exemplified by 5 to 14-membered (preferably 5 to 10-membered) (monocyclic or bicyclic) heterocyclic group having, besides carbon atom, 1 or 2 kind(s) of preferably 1 to 4 hetero atom(s) selected from nitrogen atom, sulfur atom and oxygen atom and the like. Specific examples thereof include 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-pyridazinyl, 3-isothiazolyl, 3-isooxazolyl, 1-indolyl, 2-indolyl, 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, 3-benzo[b]thienyl, 2-benzo[b]furanyl, 3-benzo[b]furanyl and the like. Preferred is oxazolyl such as 2-oxazolyl, 4-oxazolyl, 5-oxazolyl and the like.

The "substituent" of the "optionally substituted aromatic heterocyclic group" represented by R^{b16} is exemplified by 1 to 5 from the aforementioned "optionally substituted hydroxy", "optionally substituted thiol", "optionally substituted amino", "optionally substituted hydrocarbon group", "optionally substituted heterocyclic group", "acyl" and the like represented by R^{b4} or R^{b5} . Of these, optionally substituted hydrocarbon group is preferable, and C_{2-6} alkenylene substituted by optionally substituted C_{6-14} aryl is more preferable.

The amine compound such as compound (bII) can be also produced according to the method of the following Reaction b2.

(Reaction b2)

ethanol, isopropylalcohol, 2-butanol, tert-butanol, 2-methyl-2-butanol etc.), ethers (e.g., diethyl ether, diisopropy ether, tert-butylmethyl ether, diphenyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane etc.), aliphatic hydrocarbons (e.g., hexane, pentane, cyclohexane etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, chlorobenzene etc.), water, a mixture of two or more thereof and the like.

The compound (cV) thus obtained can be isolated and purified from a reaction mixture by a known method, such as concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, phase transfer, chromatography and the like.

(Reaction c3)

The compound (cV) is subjected to sulfonylation or halogenation reaction and then reacted with compound (cVI) to give compound (cVII). Specifically, compound (cV) and a sulfonylating agent or halogenating agent are reacted in an inert solvent in the presence of a base, where desired.

When the compound ~~(cIV)~~ (cVI) is on the market, a commercially available product thereof may be used as it is, or compound ~~(cIV)~~ (cVI) may be produced according to a method known per se, a method analogous thereto, and the like.

The amount of use of sulfonylating agent is about 0.1-10 equivalents, preferably 1-3 equivalents, relative to compound (cV).

The amount of use of halogenating agent is about 0.1-10 equivalents, preferably 1-3 equivalents, relative to compound (cV).

The amount of use of base is about 0.1-10 equivalents, preferably 1-3 equivalents, relative to compound (cV).

Examples of the "sulfonylating agent" include R^5-SO_2Cl such as methanesulfonyl chloride, p-toluenesulfonyl chloride etc., and the like.

Examples of the "halogenating agent" include thionyl

chloride, oxalyl chloride and the like.

Examples of the "base" include carbonate of alkali metal or alkaline earth metal (e.g., sodium carbonate, potassium carbonate etc.), hydroxide of alkali metal or alkaline earth metal (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide), organic base (e.g., diisopropylethylamine, triethylamine, pyridine etc.) and the like.

Examples of the "inert solvent" include aliphatic hydrocarbons (e.g., hexane, pentane, cyclohexane etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, chlorobenzene etc.), ethers (e.g., diethyl ether, diisopropy ether, tert-butylmethyl ether, diphenyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride etc.), esters (e.g., ethyl acetate etc.), ketones (e.g., acetone, methyl ethyl ketone etc.), nitriles (e.g., acetonitrile, propionitrile etc.), sulfoxides (e.g., dimethyl sulfoxide etc.), amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, hexamethylphosphoric triamide etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, 2-butanol, tert-butanol, 2-methyl-2-butanol etc.) and a mixture of two or more of these. Preferred are tetrahydrofuran, acetonitrile, acetone and the like.

The reaction temperature is generally from about -40°C to 100°C, preferably from about -20°C to 80°C. The reaction time is generally about 1 hour to 12 hours, preferably about 1 hour to 6 hours.

Then, the thus-obtained reaction mixture and compound (cVI) are reacted in an inert solvent in the presence of a base and(or) a phase transfer catalyst, where desired, to give compound (cVII).

When the compound ~~(cIV)~~ (cVI) is on the market, a commercially available product thereof may be used as it is, or compound

(cVI)

~~(cIV)~~ may be produced according to a method known *per se*, a method analogous thereto, and the like.

The amount of use of compound (cVI) is about 0.1-10 equivalents, preferably about 1-3 equivalents, relative to compound (cV).

The amount of use of base is about 1-100 equivalents, preferably about 1-10 equivalents, relative to compound (cV).

The amount of use of the phase transfer catalyst is about 0.01-1 equivalent, preferably about 0.01-0.3 equivalent, relative to compound (cV).

Examples of the "base" include carbonate of alkali metal or alkaline earth metal (e.g., sodium carbonate, potassium carbonate etc.), hydroxide of alkali metal or alkaline earth metal (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide) and the like.

Examples of the "phase transfer catalyst" include tetra(n-butyl)ammonium bromide, tetra(n-butyl)ammonium hydrogensulfate and the like.

Examples of the "inert solvent" include aliphatic hydrocarbons (e.g., hexane, pentane, cyclohexane etc.), aromatic hydrocarbons (e.g., benzene, toluene, xylene, chlorobenzene etc.), ethers (e.g., diethyl ether, diisopropy ether, tert-butylmethyl ether, diphenyl ether, tetrahydrofuran, dioxane, 1,2-dimethoxyethane etc.), halogenated hydrocarbons (e.g., dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride etc.), esters (e.g., ethyl acetate etc.), ketones (e.g., acetone, methyl ethyl ketone etc.), nitriles (e.g., acetonitrile, propionitrile etc.), sulfoxides (e.g., dimethyl sulfoxide etc.), amides (e.g., N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, hexamethylphosphoric triamide etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, 2-butanol, tert-butanol, 2-methyl-2-butanol etc.), water, a mixture of two or more thereof and the like. Preferred are tetrahydrofuran, acetonitrile, acetone, water and the like.

30D (methyl methacrylate-ethyl acrylate copolymer) and the like, and the like; hydrogenated oils such as hydrogenated castor oil (e.g., Lubri wax (Freund Inc.) and the like) and the like; waxes such as carnauba wax, fatty acid glycerine ester, paraffin and the like; polyglycerine fatty acid ester and the like.

As the swellable polymer, a polymer having an acidic dissociable group, which shows pH-dependent swelling, is preferable, and a polymer having an acidic dissociable group, which shows less swelling in an acidic range, such as in the stomach, but otherwise in a neutral range, such as in the small intestine and large intestine, is preferable.

Examples of the polymer having an acidic dissociable group, which shows pH-dependent swelling, include crosslinking type polyacrylic acid polymers such as Carbomer 934P, 940, 941, 974P, 980, 1342 and the like, polycarbophil, calcium polycarbophil (all mentioned above are the product of BF Goodrich), HI-BIS-WAKO 103, 104, 105, 304 (all being products of Waco Pure Chemicals Industries, Ltd.) and the like.

The film forming agent to be used for the sustained release preparation may further contain a hydrophilic material.

Examples of the hydrophilic material include polysaccharides optionally having a sulfuric acid group such as pullulan, dextrin, alkali metal salt of alginic acid and the like; polysaccharides having a hydroxy alkyl group or a carboxy alkyl group such as hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and the like; methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol and the like.

The content of the water-insoluble material of the film forming agent for a sustained release preparation is about 30 - about 90% (w/w), preferably about 35 - about 80% (w/w), more preferably about 40 - 75% (w/w), and the content of the swellable polymer is about 3 - about 30% (w/w), preferably

kneading and forming. The above-mentioned mixing can be performed by a conventional method, such as mixing, kneading and the like. Specifically, for example, when a rapid release preparation is formed into particles, a vertical granulator, a universal kneader (HATA Tekkohjo), a fluidized bed granulator FD-5S (Powrex Corporation) and the like are used for mixing, which is followed by granulating by wet extrusion granulation, fluidized bed granulation and the like, to give the preparation, as in the preparation of the core of the aforementioned sustained release preparation.

The rapid release preparation and the sustained release preparation thus obtained may be used as they are. Alternatively, after suitable separate preparation along with an excipient for a preparation and the like according to a conventional method, they may be administered simultaneously or at optional administration intervals. Alternatively, they may be each prepared into a single preparation for oral administration (e.g., granule, fine granule, tablet, capsule and the like) as they are or together with excipient for preparation and the like as appropriate. The both preparations are converted to granules or fine granules and filled in a single capsule and the like to give a preparation for oral administration.

[3] A sublingual tablet, buccal or oral cavity rapid disintegrator and preparation thereof

The sublingual tablet, buccal preparation and oral cavity rapid disintegrator may be a solid preparation such as tablet and the like or an oral cavity mucous membrane adhesion tablet (film).

As the sublingual tablet, buccal or oral cavity rapid disintegrator, a preparation containing the compound (aVa), (aVb), (bX), (6XI) or ~~(bXI)~~, (cVII) or a combination drug and an excipient is preferable. It may contain auxiliaries such as a lubricant, an isotonic agent, a hydrophilic carrier, a water dispersible

polymer, a stabilizer and the like. For easy absorption and enhanced bioavailability, β-cyclodextrin or β-cyclodextrin derivative (e.g., hydroxypropyl-β-cyclodextrin and the like) and the like may be contained.

Examples of the above-mentioned excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light anhydrous silicic acid and the like. Examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica and the like, particularly magnesium stearate and colloidal silica are preferable. Examples of the isotonicity agent include sodium chloride, glucose, fructose, mannitol, sorbitol, lactose, saccharose, glycerine, urea and the like, particularly mannitol is preferable. Examples of the hydrophilic carrier include swellable hydrophilic carriers such as crystalline cellulose, ethylcellulose, crosslinked polyvinylpyrrolidone, light anhydrous silicic acid, silicic acid, dicalcium phosphate, calcium carbonate and the like, particularly crystalline cellulose (e.g., microcrystalline cellulose and the like) is preferable. Examples of the water dispersible polymer include gum (e.g., gum tragacanth, acacia gum, guar gum), alginate (e.g., sodium alginate), cellulose derivative (e.g., methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose), gelatin, soluble starch, polyacrylic acid (e.g., carbomer), polymethacrylic acid, polyvinyl alcohol, polyethylene glycol, polyvinylpyrrolidone, polycarbofil, ascorbic palmitate and the like, with preference given to hydroxypropylmethylcellulose, polyacrylic acid, alginate, gelatin, carboxymethylcellulose, polyvinylpyrrolidone, polyethylene glycol and the like. Particularly, hydroxypropylmethylcellulose is preferable. Examples of the stabilizer include cysteine, thiosorbitol, tartaric acid, citric acid, sodium carbonate, ascorbic acid, glycine, sodium sulfite and the like, particularly, citric acid and ascorbic

acid are preferable.

The sublingual tablet, buccal and oral cavity rapid disintegrator can be produced by mixing the compound (aVa), (aVb), (bX), ~~or~~ (bXI), or (cVII), or a combination drug and an excipient by a method known *per se*. Where desired, the above-mentioned auxiliaries such as a lubricant, an isotonic agent, a hydrophilic carrier, a water dispersible polymer, a stabilizer, a coloring agent, a sweetener, an antiseptic and the like may be contained. After mixing the above-mentioned components simultaneously or with time staggering, the mixture is compression formed under pressure to give sublingual tablet, buccal or oral cavity rapid disintegrator. To achieve a suitable hardness, a solvent such as water, alcohol and the like is used to moisten or wet as necessary before and after the compression forming. After the forming, the tablets may be dried.

When a mucous membrane adhesion tablet (film) is produced, the compound (aVa), (aVb), (bX), ~~or~~ (bXI), or (cVII), or a combination drug and the above-mentioned water dispersible polymer (preferably, hydroxypropylcellulose, hydroxypropylmethylcellulose), an excipient and the like are dissolved in a solvent such as water and the like, and the obtained solution is cast to give a film. In addition, an additive such as a plasticizer, a stabilizer, an antioxidant, a preservative, a coloring agent, a buffer, a sweetener and the like may be added. To impart suitable elasticity to the film, glycols such as polyethylene glycol, propylene glycol and the like may be added, and to increase adhesion of the film to the oral cavity mucous membrane lining, bioadhesive polymer (e.g., polycarbofil, carbopol) may be added. The casting includes pouring the solution on a non-adhesive surface, spreading the solution in a uniform thickness (preferably about 10 - 1000 μ) with a coating tool such as doctor blade and the like and drying the solution to give a film. The film thus formed may be dried at room temperature or

under heating and cut into a desired surface area.

Examples of preferable oral cavity rapid disintegrator are a solid rapid diffusing administration agent having a net structure of the compound (aVa), (aVb), (bX), (bXI) or (cVII), or a combination drug and water soluble or water diffusable carrier which are inert to the compound (aVa), (aVb), (bX), (bXI) or (cVII), or a combination drug. The net structure can be obtained by sublimation of a solvent from the solid composition consisting of a solution obtained by dissolving the compound (aVa), (aVb), (bX), (bXI) or (cVII), or a combination drug in a suitable solvent.

The oral cavity rapid disintegrator preferably contains, in addition to the compound (aVa), (aVb), (bX), (bXI) or (cVII), or a combination drug, a matrix forming agent and a secondary component.

Examples of the matrix forming agent include animal proteins or vegetable proteins such as gelatins, dextrins, soybeans, wheat, psyllium seed protein and the like; rubber substances such as gum arabic, guar gum, agar, xanthan and the like; polysaccharides; alginic acids; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone and the like; a material derived from a gelatin-gum arabic complex and the like. In addition, saccharides such as mannitol, dextrose, lactose, galactose, trehalose and the like; cyclic saccharides such as cyclodextrin and the like; inorganic salts such as sodium phosphate, sodium chloride, aluminum silicate and the like; amino acid having 2 to 12 carbon atoms such as glycine, L-alanine, L-aspartic acid, L-glutamine acid, L-hydroxyproline, L-isoleucine, L-leucine, L-phenylalanine and the like are exemplified.

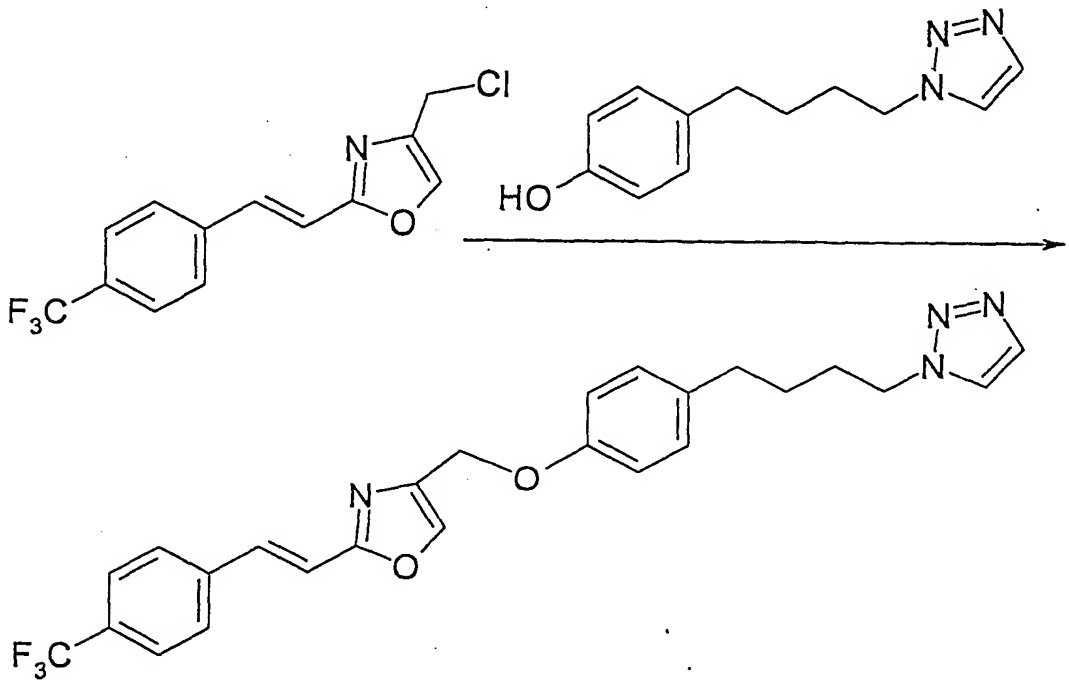
It is possible to introduce one or more matrix forming agents into a solution or suspension before preparation into a solid. Such matrix forming agent may exist with a surfactant or without a surfactant. The matrix forming agent can form a

dried under reduced pressure to give 4-(chloromethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (733 mg, yield 55%).

^{1}H-NMR ($CDCl_3$, δ, 300MHz) 4.56(2H,s), 7.01(1H,d,J=16.4Hz), 7.54-7.68(6H,m).

Reference Example 7

Production of 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]-ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole



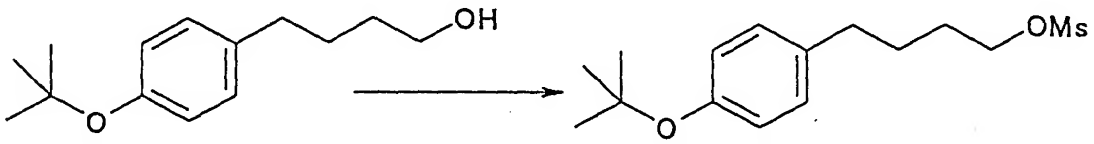
4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (400 mg, 1.84 mmol) and 4-(chloromethyl)-2-[(E)-2-[4-(trifluoromethyl)-phenyl]ethenyl]-1,3-oxazole (529 mg, 1.84 mmol) were dissolved in dimethylformamide (3 ml) and potassium carbonate (279 mg, 2.02 mmol) was added. The mixture was stirred at 65-75°C for 4 hours. 4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (40 mg, 0.184 mmol) was added and the mixture was stirred at 65-75°C for further 3 hours. The mixture was cooled to room temperature and water (5 ml) was added, then methanol (3 ml) was added. The mixture was stirred at room temperature for 40 min, and the

precipitated crystals were collected by filtration and washed with water. The crystals were dried under reduced pressure to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (799 mg, yield 93%).

^{1}H-NMR ($CDCl_3$, δ, 300MHz) 1.57-1.68(2H,m), 1.88-1.99(2H,m), 2.60(2H,t,J=7.5Hz), 4.39(2H,t,J=7.1Hz), 5.01(2H,s), 6.89-7.08(5H,m), 7.49-7.70(8H,m).

Example 5

Production of 4-[4-(tert-butoxy)phenyl]butyl methanesulfonate

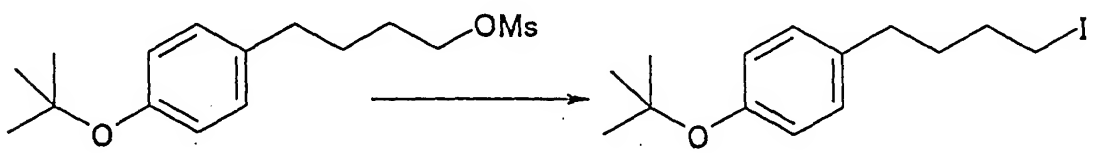


To the kolben were added 4-[4-(tert-butoxy)phenyl-butan-1-ol (70 g), triethylamine (65.2 ml) and ethyl acetate (720 ml), and the mixture was stirred. The mixture was cooled to 10°C and methanesulfonyl chloride (53.8 g) was dropwise. The mixture was stirred for 1 hour while keeping it at 5-17°C. Water (300 ml) was added and the mixture was stirred, left standing and partitioned. The organic layer was washed successively with 5% aqueous sodium hydrogen carbonate (300 ml) and water (300 ml). The organic layer was concentrated under reduced pressure to give the objective compound (102.2 g) as a concentrated residue.

^{1}H-NMR ($CDCl_3$, 300MHz) ppm: 1.33(9H,s), 1.6-1,8(4H,m), 2.62(2H, t, J=7.1), 2.99(3H,s), 4.24(2H,t,J=6.1), 6.91(2H,d,J=8.5Hz), 7.05(2H,d,J=8.5Hz)

Reference Example 8

Production of 1-tert-butoxy-4-(4-iodobutyl)benzene



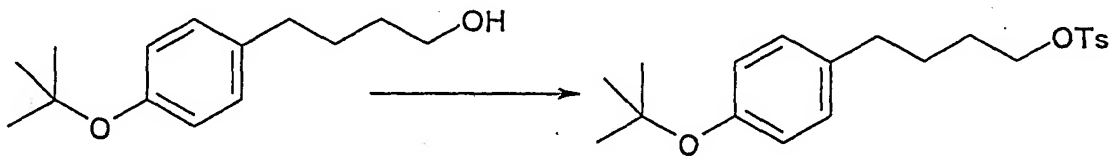
To the kolben were added 4-[4-(tert-butoxy)phenyl]butyl

methanesulfonate (33.66 g), sodium iodide (22.49 g) and acetone (337 ml), and the mixture was reacted for 1 hour by reflux under heating. To the reaction mixture were added water (500 ml) and diisopropyl ether (500 ml). After stirring, the mixture was left standing and partitioned to separate the organic layer. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate (250 ml), 10% ~~hypo~~ solution of $Na_2S_2O_3$ (250 ml) twice and water (250 ml). The organic layer was concentrated under reduced pressure to give the objective compound (35.8 g) as a concentrated residue.

^{1}H-NMR ($CDCl_3$, 300MHz) ppm: 1.33(9H,s), 1.6-1.7(2H,m), 1,8-1.9(2H,m), 2.59(2H,t,J=7.5Hz), 3.20(2H,t,J=6.9Hz), 6.90(2H,d,J=8.4Hz), 7.04(2H,d,J=8.4Hz)

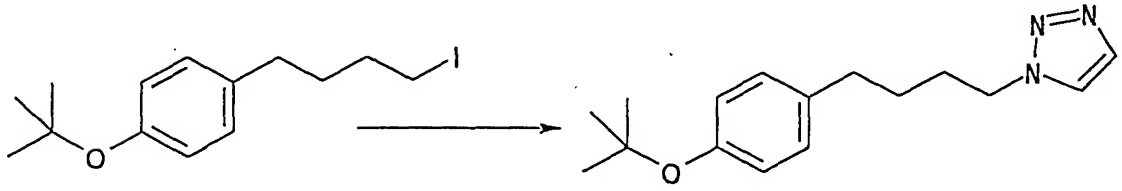
Example 6

Production of 4-[4-(tert-butoxy)phenyl]butyl (4-methylbenzene)-sulfonate



To the kolben were added 4-[4-(tert-butoxy)phenyl-butan-1-ol (5.28 g) and pyridine (9 ml), and the mixture was stirred. Toluenesulfonyl chloride (5.70 g, 1.5 eq) was added at an inner temperature of 5°C and the mixture was allowed to react at room temperature for 2 hours. Water (20 ml) was added at not higher than 10°C and the mixture was stirred for 5 min. Ethyl acetate (40 ml) was added and the aqueous layer was separated. The organic layer was washed with 10% aqueous boric acid (20 ml) three times and with water (20 ml) once. The organic layer was concentrated under reduced pressure to give a concentrated residue (8.80 g) of the objective compound.

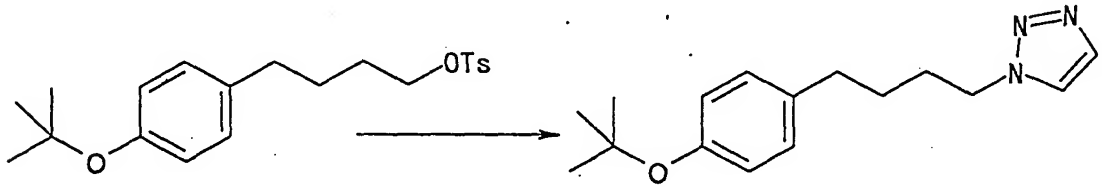
This was applied to silica gel chromatography and the effective fraction was concentrated to give the objective compound (6.40 g).



To the kolben were added sodium hydroxide (3.0 g), 1H-1,2,3-triazole (5.18 g) and 2-methyl-2-butanol (20 ml), and the mixture was refluxed under heating for 1 hour (inner temperature then was 100-102°C). A solution of 1-tert-butoxy-4-(4-iodobutyl)benzene (17.9 g)/2-methyl-2-butanol (20 ml) was added dropwise over about 1 hour 50 min. The mixture was reacted at the same temperature for 3 hours. After cooling, the mixture was concentrated. To the residue were added water (20 ml) and toluene (20 ml), and the mixture was stirred. After standing and partitioning, the organic layer was washed with 5% aqueous sodium hydrogen carbonate (20 ml) and then with water (20 ml). The organic layer was concentrated to give objective compound (15.6 g) as a concentrated residue.

Example 11

Production of 1-[4-(4-tert-butoxyphenyl)butan-1-yl]-1H-1,2,3-triazole

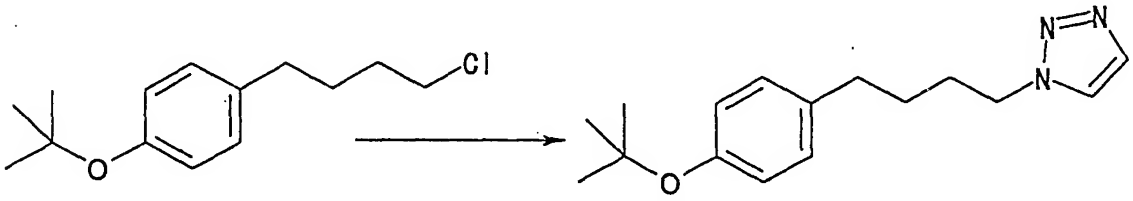


To the kolben were added 1H-1,2,3-triazole (1.65 g), sodium iodide (3.58 g), sodium hydroxide (0.96 g) and 2-methyl-2-butanol (7 ml), and the mixture was refluxed under heating for 1 hour (inner temperature then was 100-102°C). A solution of 4-[4-(tert-butoxy)phenyl]butyl (4-methylbenzene)~~phosphonate~~ sulfonate (6.00 g)/2-methyl-2-butanol (7 ml) was added dropwise over about 1 hour. The mixture was reacted at the same temperature for 3 hours. After cooling, the mixture was concentrated. To the

residue were added water (10 ml) and toluene (20 ml), and the mixture was stirred. After standing and partitioning, the organic layer was washed with 5% aqueous sodium hydrogen carbonate (10 ml) and then with water (10 ml). The organic layer was concentrated to give objective compound (4.10 g) as concentrated residue.

Example 12

Production of 1-[4-(4-tert-butoxyphenyl)butan-1-yl]-1H-1,2,3-triazole



To the kolben were added 1H-1,2,3-triazole (5,18 g), sodium iodide (7.48 g), sodium hydroxide (3.0 g) and 2-methyl-2-butanol (20 ml), and the mixture was refluxed under heating for 1 hour. A solution of 1-tert-butoxy-4-(4-chlorobutyl)benzene (12.04 g)/2-methyl-2-butanol (20 ml) was added dropwise over about 2 hours, and the mixture was reacted at inner temperature 100-102°C for 2 hours. Water (20 ml) and toluene (20 ml) was added and the mixture was stirred, left standing and partitioned to separate the aqueous layer. The organic layer was washed successively with 5% aqueous sodium hydrogen carbonate (20 ml) and water (20 ml). The organic layer was concentrated to give the objective compound (13.55 g) as a concentrated residue.

Reference Example 9

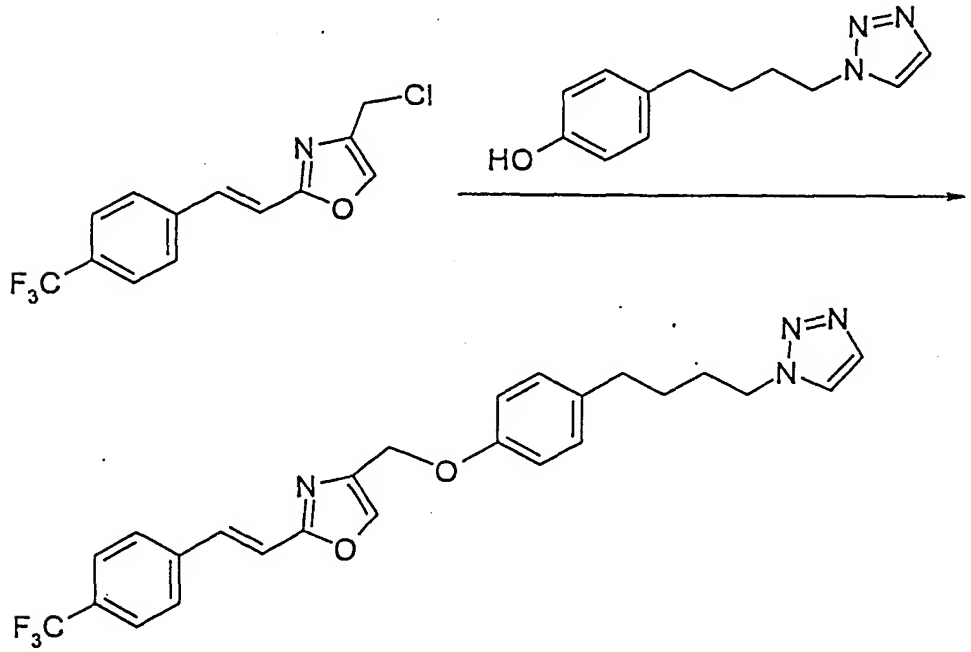
Production of 4-[4-(1H-1,2,3-triazol-1-yl)butyl]phenol

dichloroacetone (1.1 g, 8.66 mmol) were added to toluene (5 ml) and the mixture was refluxed under heating for 8 hours. Ethyl acetate (20 ml) was added, and the mixture was washed with water (20 ml) twice and concentrated under reduced pressure. To the residue was added methanol (4 ml) and the mixture was stirred at room temperature. The crystals were filtrated and dried under reduced pressure to give 4-(chloromethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (733 mg, yield 55%).

^{1}H-NMR ($CDCl_3$, δ, 300MHz) 4.56(2H,s), 7.01(1H,d,J=16.4Hz), 7.54-7.68(6H,m).

Reference Example 16

Production of 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]-ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole



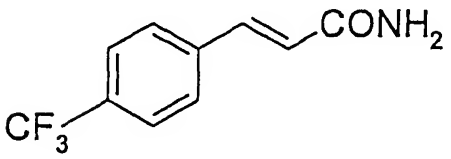
4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (400 mg, 1.84 mmol) and 4-(chloromethyl)-2-[(E)-2-[4-(trifluoromethyl)-phenyl]ethenyl]-1,3-oxazole (529 mg, 1.84 mmol) were dissolved in dimethylformamide (3 ml), potassium carbonate (279 mg, 2.02 mmol) was added and the mixture was stirred at 65-75°C for 4

hours. 4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (40 mg, 0.184 mmol) was added and the mixture was stirred at 65-75°C for 3 more hours. After cooling to room temperature, water (5 ml) and methanol (3 ml) were added in this order, and the mixture was stirred at room temperature for 40 min. The precipitated crystals were collected by filtration, washed with water and dried under reduced pressure to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]-butyl]-1H-1,2,3-triazole (799 mg, yield 93%).

^{1}H-NMR ($CDCl_3$, δ, 300MHz) 1.57-1.68(2H,m), 1.88-1.99(2H,m), 2.60(2H,t,J=7.5Hz), 4.39(2H,t,J=7.1Hz), 5.01(2H,s), 6.89-7.08(5H,m), 7.49-7.70(8H,m).

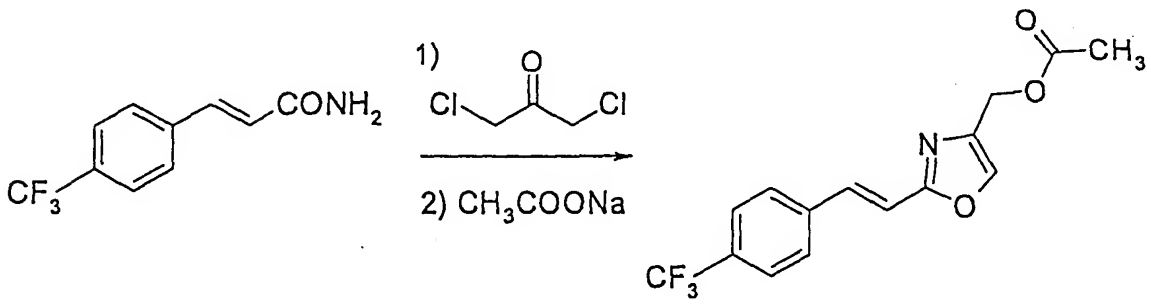
Reference Example 17

(E)-3-(4-(Trifluoromethyl)phenyl)-2-propenamide



(E)-3-(4-(Trifluoromethyl)phenyl)-2-propenoic acid (2400 g, 11.1 mol) and DMF (N,N-dimethylformamide)(82 ml) were added to toluene (12 L). $SOCl_2$ (52.6 mL, 721 mmol) was added dropwise at room temperature and the mixture was stirred at 45-50°C for 1 hour. The toluene solution cooled to room temperature was added dropwise to 25% aqueous ammonia (12L) at 5-25°C. The mixture was stirred at 45-55°C for 1 hour. After allowing to cool to room temperature and stirring, the mixture was stirred at the same temperature for 1 hour. The precipitated crystals were collected by filtration, washed with water (12 L) and dried under reduced pressure to give (E)-3-(4-(trifluoromethyl)phenyl)-2-propenamide (2293 g, 10.7 mol, yield 96%).

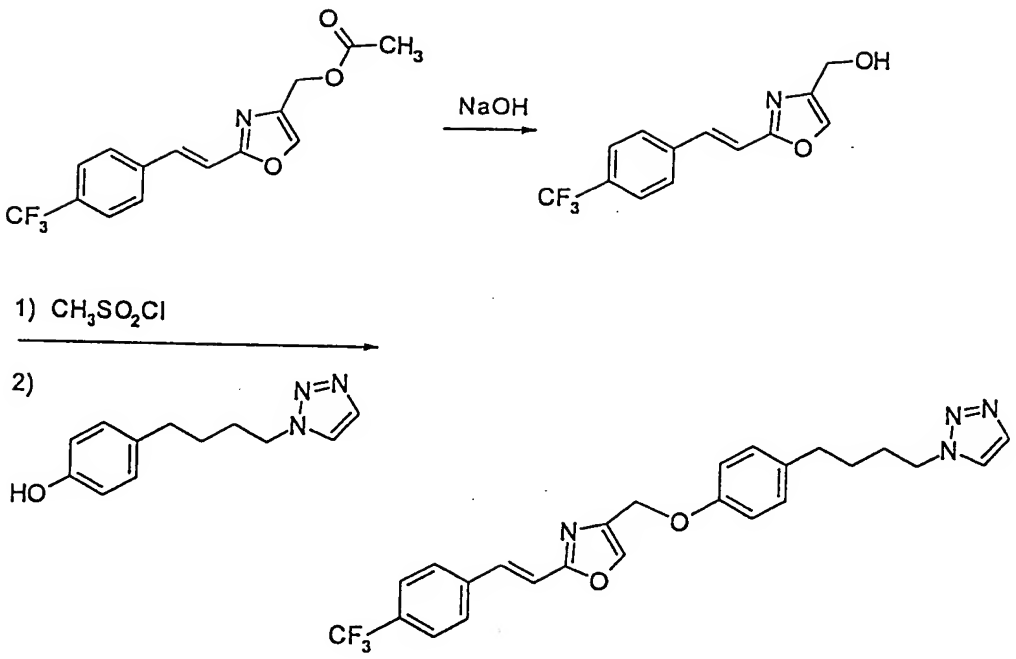
^{1}H-NMR (DMSO-d_6, δ, 300MHz) 6.72(1H,d,J=16.1Hz), 7.20(1H,s), 7.46(1H,d,J=15.9Hz), 7.62(1H,s), 7.67-7.83(4H,m).



(E)-3-(4-(Trifluoromethyl)phenyl)-2-propenamide (950 g, 4.42 mol) and 1,3-dichloroacetone (1045 g, 8.23 mol)were added to toluene (4.75 L) and the mixture was subjected to refluxing azeotropic dehydration using a Dean-Stark tube for 8 hours. During the reaction, an azeotropic mixture (2.38 L) was removed. The reaction mixture was concentrated under reduced pressure, and dimethyl sulfoxide (4.75L) and sodium acetate (905 g, 11.0 mol) were added to the residue. The mixture was stirred at 70-80°C for 3.5 hours. Methanol (4.75 L) was added. After allowing to cool to room temperature and stirring, the mixture was stirred for 1 hour under ice-cooling. The precipitated crystals were collected by filtration, washed with cold-methanol (1.9 L), and dried under reduced pressure to give 4-(acetoxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (1560 g, yield 51%).

Example 27

1-[4-[4-[[2-[(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole



4-(Acetoxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]-ethenyl]-1,3-oxazole (20.0 g, 64.3 mmol) was dissolved in dimethyl sulfoxide (200 ml), and 2N-aqueous sodium hydroxide solution (35 mL, 70.0 mmol) was added at 50°C. The mixture was stirred at about 40°C for 15 min. Water (200 ml) was added at the same temperature. After allowing to cool to room temperature and stirring, the mixture was stirred at the same temperature for 1 hour. The precipitated crystals were collected by filtration, washed with water (60 ml) and dried under reduced pressure to give 4-(hydroxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (16.4 g, 61.1 mmol, yield 95%).

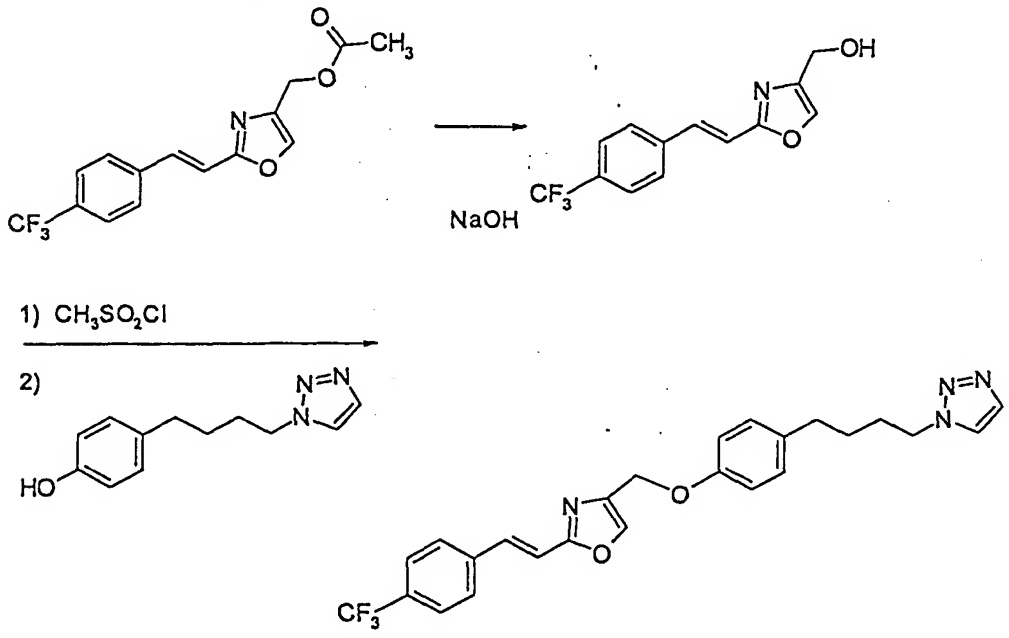
The obtained 4-(hydroxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (1.00 g, 3.71 mmol) and diisopropylethylamine (0.95 mL, 5.44 mmol) were added to THF (tetrahydrofuran) (15 ml). Methanesulfonyl chloride (0.45 mL, 5.81 mmol) was added dropwise under ice-cooling. The mixture was stirred at the same temperature for 1 hour. 4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (900 mg, 4.14 mmol) and tetra(n-butyl)ammonium bromide (60 mg, 0.19 mmol) were added at

the same temperature. A 2N aqueous sodium hydroxide solution (7.5 mL, 15.0 mmol) was added dropwise at not more than 15°C and the mixture was stirred with reflux for 1 hour. After allowing to cool to room temperature and stirring, the organic layer was concentrated under reduced pressure. Ethanol (20 ml) was added to the residue, and the mixture was stirred with reflux. Water (20 ml) was added dropwise at the same temperature. After allowing to cool to room temperature and stirring, the mixture was ice-cooled. The precipitated crystals were collected by filtration, washed with water (20 ml) and dried under reduced pressure to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (1.61 g, 3.44 mmol, yield 88%).

^{1}H-NMR ($CDCl_3$, δ, 300MHz) 1.57-1.68(2H,m), 1.88-1.99(2H,m), 2.60(2H,t,J=7.5Hz), 4.39(2H,t,J=7.1Hz), 5.01(2H,s), 6.89-7.08(5H,m), 7.49-7.70(8H,m).

Example 28

1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole



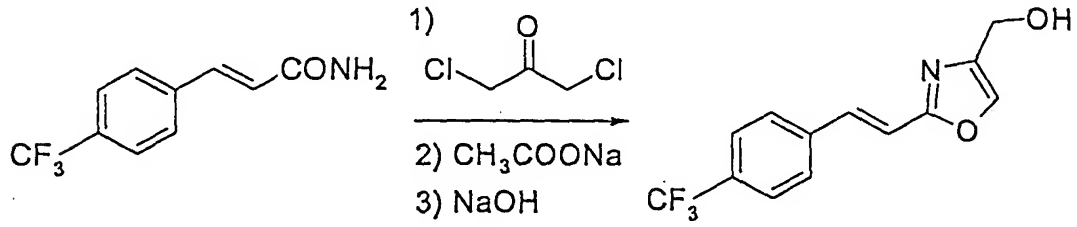
4-(Acetoxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]-ethenyl]-1,3-oxazole (1556 g, 2.23 mol), 2N-aqueous sodium hydroxide solution (2.4 L, 4.8 mol) and activated carbon (47 g) were added to methanol (4.7 L), and the mixture was refluxed under stirring for 1 hour. The activated carbon and the insoluble material were removed by filtration under pressurization. The residue was washed with methanol/water (2:1) (470 ml). The washing solution was combined with the filtrate and the mixture was refluxed. Water (3.3 L) was added at the same temperature. After allowing to cool to room temperature and stirring, the mixture was stirred at the same temperature for 1 hour. The precipitated crystals were collected by filtration, washed with water (4.7 L) and dried under reduced pressure to give 4-(hydroxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (568.5 g, 2.11 mol, yield 95%).

The obtained 4-(hydroxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole (567 g, 2.11 mol) and diisopropylethylamine (340 g, 2.63 mol) were added to THF (3.4 L). A solution of methanesulfonyl chloride (302 g, 2.63 mol) in THF (567 ml) was added dropwise under ice-cooling. The mixture was stirred at the same temperature for 1 hour and diisopropylethylamine (27.3 g, 0.21 mol), methanesulfonyl chloride (24. 2g, 0.21 mol) and THF (57 ml) solution were added. The mixture was stirred under reflux for 1.5 hours. After allowing to cool to room temperature, 15% aqueous sodium hydroxide (1.96 kg, 7.35 mol) was added dropwise. 4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (503 g, 2.32 mol) and tetra(n-butyl)ammonium bromide (68.0 g,0.21 mol) were added at the same temperature, and the mixture was refluxed for 4 hours under stirring. Water (3.1 L) and methanol (7.4 L) were added dropwise at the same temperature. After allowing to cool to room temperature, the mixture was stirred at the same temperature for 1 hour. The precipitated crystals were

collected by filtration, washed with THF/methanol/water (1:1:2) (2.8 L), water (2.8 L) and cold-methanol (2.8 L) and dried under reduced pressure to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]-butyl]-1H-1,2,3-triazole (883 g, 1.88 mol, yield 85%).

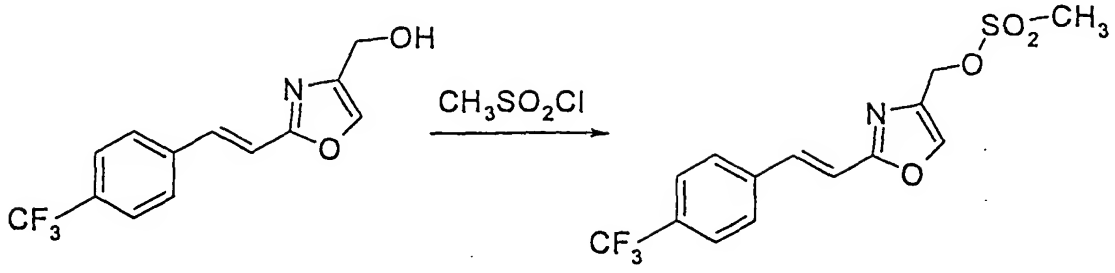
Reference Example 18

4-(Hydroxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazole



(E)-3-(4-(Trifluoromethyl)phenyl)-2-propenamide (20.0 g, 92.9 mmol) was added to toluene (75 ml), and 1,3-dichloroacetone (22.0 g, 173.3 mmol) and toluene (25 ml) were added. The mixture was subjected to refluxing azeotropic dehydration for 9 hours. The reaction mixture was divided into two equal portions and one of them was concentrated under reduced pressure. To the residue were added dimethyl sulfoxide (100 ml), sodium acetate trihydrate (15.9 g, 116.8 mmol) and water (20 ml). The mixture was stirred at 70-75°C for 4.5 hours. 2N-Aqueous sodium hydroxide solution (60 ml) was added at the same temperature and the mixture was stirred for 1 hour. After allowing to cool to room temperature, toluene (400 ml) and water (400 ml) were added and the mixture was partitioned. After washing with 5% brine (200 ml), the organic layer was concentrated under reduced pressure. To the residue was added methanol (10 ml) and the mixture was heated to 60°C to allow dissolution. After allowing to cool to room temperature and stirring, the mixture was stirred for 1 hour under ice-cooling. The precipitated crystals were collected by filtration, washed with cold-methanol (5 ml) and dried under reduced pressure to

yl]methylmethanesulfonate

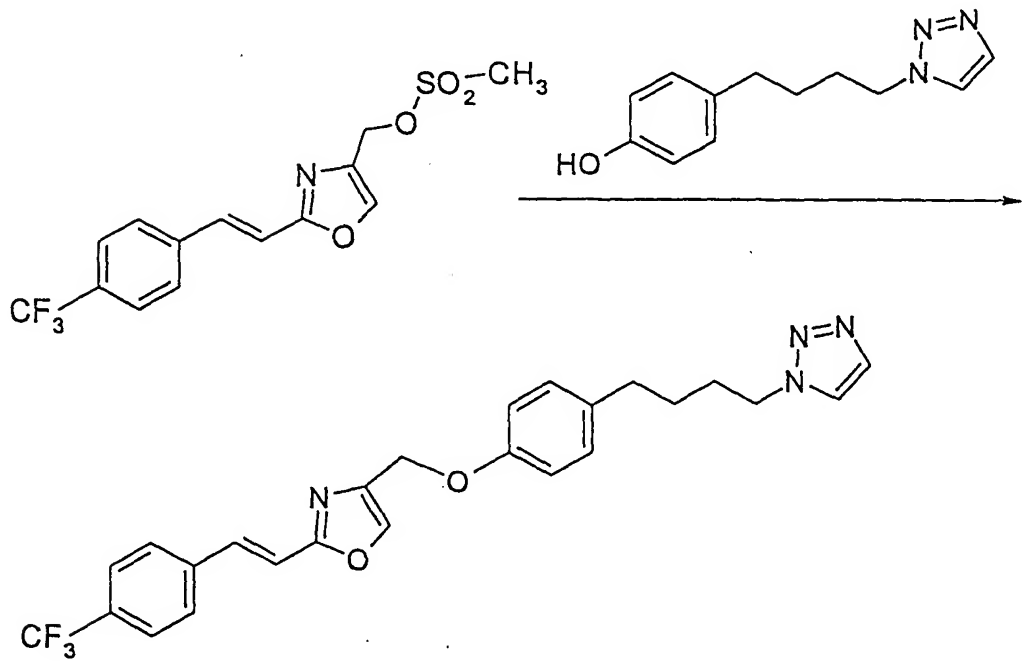


4-(Hydroxymethyl)-2-[(E)-2-[4-(trifluoromethyl)phenyl]-ethenyl]-1,3-oxazole (5.0 g, 18.6 mmol) and triethylamine (3.1 mL, 22.4 mmol) were added to THF solution (25 ml), and methanesulfonyl chloride (1.8 mL, 23.3 mmol) was added dropwise under ice-cooling. THF (25 ml) was added at the same temperature and the mixture was stirred for 40 min. The mixture was stirred at room temperature for 1 more hour. To the mixture was added water (25 ml) and the mixture was extracted with ethyl acetate (25 ml). The organic layer was washed with water (25 ml). The aqueous layers were combined and extracted with ethyl acetate (25 ml). The organic layers were combined and concentrated. Ethyl acetate (40 ml) and isopropyl ether (10 ml) were added to the residue. The mixture was heated to 60°C for dissolution. After allowing to cool to room temperature with stirring, isopropyl ether (10 ml) was added under ice-cooling and the precipitated crystals were collected by filtration. The crystals were washed with isopropyl ether (10 ml) and dried under reduced pressure to give [2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methylmethanesulfonate (5.1 g, 14.5 mmol, yield 78%).

^{1}H-NMR ($CDCl_3$, δ, 300MHz) 3.09(3H,s), 5.22(1H,s), 7.00(1H,d,J=16.4Hz), 7.57(1H,d,J=16.4Hz), 7.60-7.69(4H,m), 7.78(1H,s).

Reference Example 21

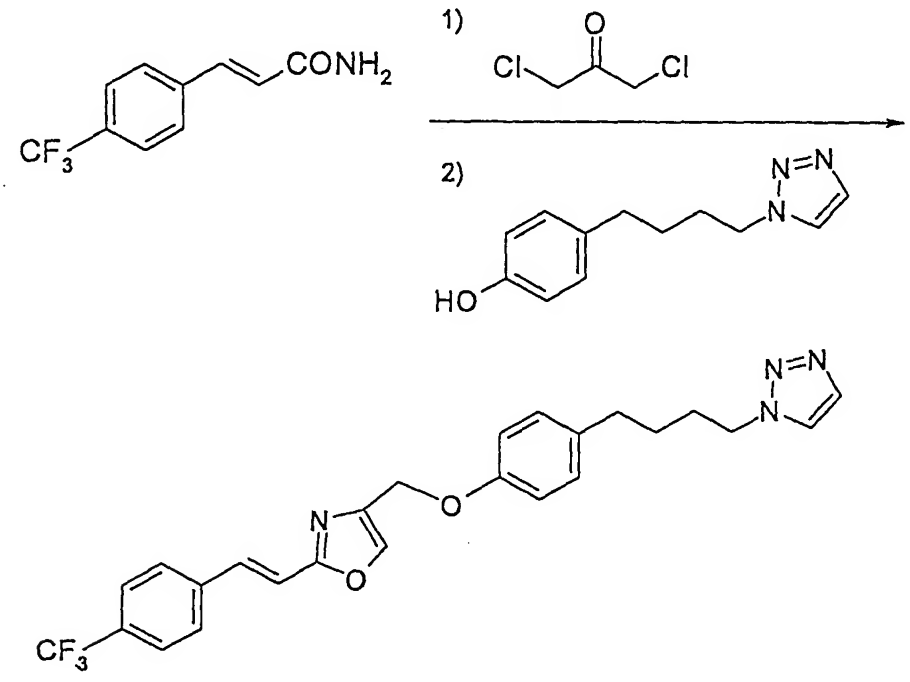
1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole



[2-[(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methylmethanesulfonate (500 mg, 1.44 mmol), 4-[4-(1H-1,2,3-triazol-1-yl)butyl]phenol (344 mg, 1.58 mmol) and tetra(n-butyl)ammonium bromide (45 mg, 0.14 mmol) were added to THF (5 ml), and 1N-aqueous sodium hydroxide solution (3.0 mL, 3.00 mmol) was added. The mixture was stirred at room temperature for 5 hours. 10% Brine (10 ml) was added and the mixture was extracted with ethyl acetate (10 ml). The organic layer was washed with 10% brine (10 ml). The aqueous layers were combined and extracted with ethyl acetate (10 ml). The organic layers were combined and concentrated. Ethanol (15 ml) was added to the residue and the mixture was refluxed under heating for dissolution. After allowing to cool to room temperature and stirring, the mixture was stirred for 1 hour under ice-cooling. The precipitated crystals were collected by filtration, washed with cold-ethanol (2 ml) and dried under reduced pressure to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (556 mg, 1.19 mmol, yield 81%).

Example 29

1-[4-[4-[[2-[(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole



(E)-3-(4-(Trifluoromethyl)phenyl)-2-propenamide (4.00 g, 18.59 mmol) and 1,3-dichloroacetone (3.54 g, 27.89 mmol) were added to toluene (14 ml) and the mixture was subjected to refluxing azeotropic dehydration using a Dean-Stark tube for 3 hours. A solution of sulfuric acid (91 mg) in toluene (1 ml) was added at the same temperature and the mixture was further subjected to refluxing azeotropic dehydration for 3.5 hours. The reaction mixture was concentrated under reduced pressure, and THF (20 ml) and tetra(n-butyl)ammonium bromide (428 mg, 1.328 mmol) were added to the residue. 30% Aqueous potassium hydroxide solution (12.42 g, 66.4 mmol) was added dropwise at 20-30°C and the mixture was stirred at the same temperature for 15 min. 4-[4-(1H-1,2,3-Triazol-1-yl)butyl]phenol (2.89 g, 13.28 mmol) was added and the mixture was refluxed under stirring for 2 hours. Water (13.4 ml) and methanol (20 ml) were added dropwise at the same temperature. After allowing to cool to

room temperature and stirring, the mixture was stirred at the same temperature for 1 hour. The precipitated crystals were collected by filtration, washed with cold-methanol (40 ml) and dried under reduced pressure to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (5.35 g,11.42 mmol, yield 86%).

Reference Example 22

Production of 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)-phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole

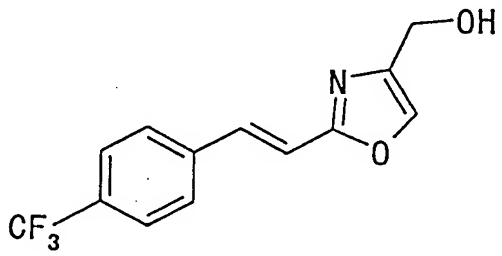
1-[4-[4-[[2-[(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole (5.0 g) was added to water/1-propanol=1/9 (65 ml), and active charcoal (100 mg) was added. After refluxing under heating, an insoluble material was filtered off while hot, and the residue was washed with water/1-propanol=1/9 (5 ml). The filtrate was refluxed again and was allowed to cool and stirred at 50°C to 55°C for 30 min. Water (56 ml) was added dropwise at the same temperature and the mixture was stirred at from 50°C to 60°C for 20 hours. The crystals were filtrated, washed with water (50°C) and dried under reduced pressure at 40°C to give 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]-phenyl]butyl]-1H-1,2,3-triazole (4.29 g, yield 92%) as crystals (the same crystals as those obtained in Example 4 of Japanese Patent Application No. 2000-108204).

The crystals were analyzed by powder X ray diffraction, the results of which are shown in the following.

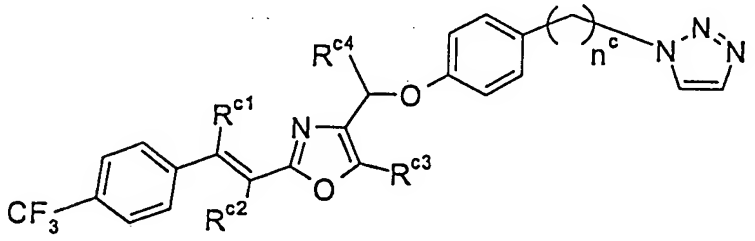
The crystals showed a powder X ray diffraction pattern showing characteristic peaks at diffraction angles (2θ) of powder X ray diffraction of 15.88, 21.22 and 21.82 degrees. The powder X ray diffraction chart is shown in Fig. 1.

Example 30

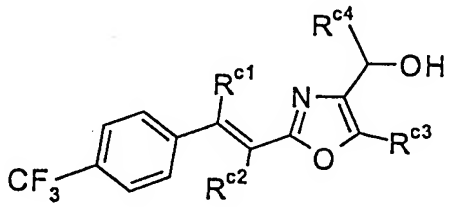
Production of 1-[4-[4-[[2-[(E)-2-[4-(trifluoromethyl)-



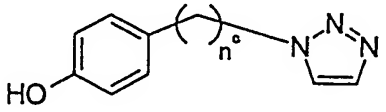
45. A method for producing a compound of the formula



wherein n^c is an integer of 1 to 10 and other symbols are as defined in claims 32, or a salt thereof, which comprises subjecting a compound of the formula



wherein each symbol is as defined above, or a salt thereof to sulfonylation or halogenation, and reacting the resulting compound with a compound of the formula



wherein n^c is as defined above, or a salt thereof.

(Amended)

46. 1-[4-[4-[[2-[(E)-2-[4-(Trifluoromethyl)phenyl]ethenyl]-1,3-oxazol-4-yl]methoxy]phenyl]butyl]-1H-1,2,3-triazole.

47. The crystal of claim 46, having characteristic peaks at diffraction angles of 6.98, 14.02, 17.56, 21.10 and 24.70